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TITLE: Study of Current Practice and Future Advancements in Blood Management and Effectiveness of a Multimodality Training Program on Improving Transfusion Knowledge, Practice and Outcomes

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14. ABSTRACT Allogeneic (donor) blood transfusions can save lives when treating blood loss due to trauma, surgery or disease. But transfusions carry risks. Current practices are often sub-optimal, and many patients are inappropriately transfused. This research goal is to improve transfusion practice by creating and testing an evidenced based Patient Blood Management (PBM) curriculum. To identify best practices, investigators have analyzed over 300,000 peer reviewed manuscripts and encapsulated these findings into a computerized, online knowledge repository of documented PBM best practices. The team concurrently developed a state of the art, multi-modality PBM curriculum that translates the evidenced based findings into clinical best practice training. The budget for this five year study was reduced to three years midway thru its execution. Consequently, the research was limited to: 1) Configuring, building and populating the evidenced based PBM knowledge repository; and 2) Developing the multi-modality training curriculum. Testing of the tools will have to be pursued in future research. The study, though lacking the budgeted funds necessary to fully realize its original objectives, has produced three important deliverables: 1) A one of a kind, comprehensive PBM best practice knowledgebase; 2) An associated PBM multi-modality curriculum to translate evidence based best practices to clinical standards of care; and, 3) produced advanced simulation PBM training tools which can measurably enhance PBM best practice skill acquisition.									
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Introduction

Allogeneic (donor) blood transfusion can be life-saving. It is used to treat blood loss due to trauma, surgery or blood diseases such as anemia, hemophilia or sickle-cell disease. But transfusions carry risks. Current practices are often sub-optimal, and many patients are inappropriately transfused. Patient Blood Management (PBM) embodies strategies to manage and conserve patients' blood and reduce the need for donor blood. PBM optimizes hemoglobin level, minimizes blood loss, and uses transfusions according to evidence-based criteria. There is evidence that PBM leads to better outcomes for patients, reduces costs, and facilitates patient care despite blood shortages. *This research's original objective was to test the hypothesis that evidenced-based, multi-modality training improves transfusion practice and patient outcomes. During the course of this investigation the research team has configured, deployed and populated an evidenced based PBM knowledge repository, developed a multi-modality PBM curriculum and devised PBM simulation systems to enhance skill acquisition and retention.*

The transfusion status quo is unacceptable as it exposes millions of patients to avoidable risks, and burdens the health care system with billions of dollars in unnecessary expenses annually. Transfusion is unique in that despite its widespread use, there is a wide gap between evidence and practice. This study will serve as a model of training in PBM and serve our military and public interests by reducing unjustified transfusions, providing alternatives when blood is not available, reducing healthcare costs, and alleviating shortages in blood supply.

Body

This research effort has been designed to test the militarily relevant hypothesis that a multi-modality PBM training program will improve transfusion practice and patient outcomes across a wide variety of clinical settings. This is achieved by equipping health care providers with a multi-modality training program that provides an evidence-based framework of strategies to minimize the need for transfusion.

This project has the following specific aims:

- 1) Develop an evidence-based multimodality PBM training program;
- 2) Compare transfusion knowledge of study participants before and after training;
- 3) Compare transfusion practice of participants before and after training; and
- 4) Compare outcomes in patients cared for by participants before and after training.

Changes in legislative processes impacting federal appropriations resulted in a reduction of the original study budget from 5 years to 3. Accordingly, the research team has focused on optimizing the evidenced based *patient blood management data repository, related multi-modality training curriculum, and PBM simulation systems* to meet military requirements. As a result, the team has taken concrete steps to engage military stakeholders in identifying military blood management priorities and aligning research efforts to deliver lasting value in the event that Year 4 and 5 funds were unavailable to execute the 3 cycles of pre and post data collection and analysis, *as originally planned*. Draft study protocol is shown at Appendix A.

Key Research Accomplishments

During this reporting period, investigators completed the PBM literature review, database and curriculum development. This provides a robust, and unique, bibliography, content, structure, and delivery mechanisms for state of the art blood management education and outreach. Thru the period covered by this report, the EHMC team analyzed **575,000** blood transfusion and PBM scholarly manuscripts indexed in PubMed for inclusion in the evidenced based curriculum literature depository and database (Appendix A)

As noted in earlier reports, continuous review of the most recent medical literature *has been* an essential element to ensure that the most recent evidence is incorporated into the PBM training materials. Core parameters of the evidence pools are established, and the objective has been to compile a comprehensive and continuously updated searchable database of the research papers focusing on PBM.

Research papers could be primary (i.e. original research) or secondary (i.e. meta-analysis or systematic reviews). Consensus statements and evidence-based guidelines/recommendations were also included. To be eligible, the papers had to provide data on any of the PBM techniques (e.g. modalities to promote body ability to produce blood, prevent/minimize unnecessary blood loss, and recover and reuse patient's own blood). During this report period, various databases of medical literature were examined with focus on articles indexed in PubMed as the primary source for the PBM articles.

The search strategy conformed to the following criteria: 1) A comprehensive set of key word searches verified to yield desired results following extensive testing; 2) PubMed searches using key words to identify eligible studies; 3) Eligible PubMed papers reviewed against a detailed set of inclusion and exclusion criteria downloaded in to Reference Manager; 4) Papers organized according to the PBM techniques and key study parameters (including the quality of evidence ratings) and main outcomes will be extracted into a searchable database.; 5) Repeating steps 2-4 for new papers indexed in PubMed after the date of the initial search to identify the new studies. Specifically, alerts were created in PubMed using the same keywords used in step 2 above to alert the study personnel of any new potentially.

The PBM literature depository now provides a unique resource that directly supports state of the art best practices in **28 blood management priority topic areas** including transfusion science, blood utilization, hemostatic management, coagulopathy, and blood substitutes.

In addition, EHMC convened the "**Novel Ideas for Resuscitation and Severe Hemorrhage Care**" DOD/NIH workshop at its facilities on 31 August 2011. The full day symposia and working session included participation from key blood management program managers from the U.S. Army Medical Research and Material Command (USAMRMC), DARPA (Defense Advanced Research Projects Agency), U.S. Navy, and NIH (National Institutes of Health).

The meeting was is-designed to provide an opportunity for key DOD and NIH stakeholders to assess the progress of the repository and curriculum development process, and optimize relevance to military blood management research priorities. The end state objective was is to

optimize the value of the repository and curriculum to evolving military blood management requirements. This meeting followed-up on numerous correspondence and teleconferences conducted by DOD and EHMC personnel during the reporting period indicating strong potential intersections between the DARPA ‘**Surviving Blood Loss (SBL)**’ and the EHMC “**Bloodless**” programs.

31 August 2011 participants included:

- Dr Jon Mogford, Ph.D., Acting Director, Defense Sciences Office, Defense Advanced Research Projects Agency (DARPA) – Telephonic
- Douglas Duchak, President and *CEO*, Englewood Hospital and Medical Center (EHMC)
- Dr Aryeh Shander, MD, FCCM, FCCP, Chief of Department of Anesthesiology, Critical Care and Hyperbaric Medicine, EHMC
- Dr Kaveh Zamani, Ph.D., Consultant, DARPA and Walter Reed Army Institute of Research (WRAIR), U.S. Army Medical Research and Material Command (USAMRMC)
- Dr. Anthony E. Pusateri, Ph.D., Hemorrhage Control Research Program, USAMRMC
- COL Richard Gonzales, Blood Products Manager, US Army Medical Material Development Activity (USAMMDA), USAMRMC
- CDR Roland Fahie, Director, Navy Blood Program, Bureau of Medicine (BUMED)
- Dr. George Sopko, M.D., MPH, “Resuscitation Outcomes Consortium” (ROC), National Heart, Lung and Blood Institute (NHLBI), National Institutes of Health (NIH)
- Dr. Carl C. Peck, M.D., (Founder and CEO of NDA Partners and the Founding Director of the Center for Drug Development Science, UCSF, former Director of the U.S. FDA Center for Drug Evaluation and Research, former Assistant Surgeon General of the United States
- Dr. D. Bruce Burlington, M.D., Consultant, pharmaceutical product development and regulatory affairs, former Executive Vice President, Wyeth, former Director Center for Devices and Radiological Health, former, Director, Division of Biological Investigational New Drugs, FDA.
- Dr. Mazyar Javidroozi, M.D., Institute for Patient Blood Management & Bloodless Medicine and Surgery, EHMC
- Dr. John Sokolowski, Ph.D., Virginia Modeling, Analysis and Simulation Center, Old Dominion University (ODU)
- Mr. Wilbur Malloy, Program Manager, Blood Products and Safety, Telemedicine and Advanced Technology Research Center (TATRC), USAMRMC
- Ms. Anna Juhl, R.N., Institute for Patient Blood Management & Bloodless Medicine and Surgery, EHMC
- Mr. Conrad Clyburn, Consultant, EHMC

To further strengthen the EHMC training offering the program has entered into an collaboration agreement with Old Dominion University to leverage its multi-media simulation tools to accelerate PBM skill acquisition and sustainment. The ODU technology *enables* the unique EHMC blood management curriculum to be effectively deployed in an Advanced Distributed Learning (ADL) – Just in Time (JIT) mode. An option which some analysts have noted may be necessary to effectively meet the needs of healthcare providers with constrained schedules.

EHMC investigators also continued their strategy of participating in military medicine specific scientific and clinical symposia to facilitate enhanced alignment of their training curriculum with military requirements. As part of this strategy, EHMC was one of the few civilian medical centers to attend the annual USAMRMC sponsored ATACCC (Advanced Technology Applications for Combat Casualty Care) in August 2011.

The core features of the PBM curriculum that resulted from these processes are captured in the curriculum’s statement of purpose and overall goals. These include to: 1) teach the needed

knowledge and develop the needed skills of health care providers and administrators to be able to provide comprehensive PBM; 2) provide the legal and ethical background needed to provide standard of care PBM; 3) sensitize the trainee for the benefits of a multidisciplinary PBM and the overall goal of transfusion avoidance; 4) develop an attitude of patient-centered care; 5) animate the participants in the class to put their newly-gained knowledge into practice; and; 6) start the process of continuing education in the field of PBM.

Content and organization: The topics covered in the curriculum include:

A: Historical Background

Topic 1: History of Blood Management

B: Scientific Basis of Blood Management

Topic 2: Scientific Basis of Blood Management – Physiology

Topic 3: Scientific Basis of Blood Management – Pathophysiology

C: Diagnostic Procedures in Blood Management

Topic 4: Diagnosis of Red cell disorders and oxygen carrying capacity

Topic 5: Diagnosis of Disorders in homeostasis

Topic 6: Diagnosis of Blood Volume Replacement

D: Techniques to reduce patient's exposure to donor blood

Topic 6: Use of Autologous blood

Topic 7: Extracorporeal circulation

Topic 8: Surgical Measures to reduce blood loss

E: Pharmacology of Blood Management

Topic 9: Enhancement of Erythropoiesis

Topic 10: Enhancement of Coagulation

Topic 11: Enhancement of Leukopoiesis

Topic 12: Fluid resuscitation

Topic 13: Artificial Oxygen Carriers

Topic 14: Oxygen therapy

F: Transfusion Medicine Aspects of Blood Management

Topic 15: Laboratory Transfusion Medicine

Topic 16: Clinical Transfusion Medicine

G: Organization and Legal Aspects of Blood Management

Topic 17: Organization of blood management

Topic 18: Legal and ethical aspects of blood management

H: Specific Measures of Transfusion Avoidance

Topic 19: Measures of transfusion avoidance: Anesthesiology

Topic 20: Measures of transfusion avoidance: Emergency Medicine

Topic 21: Measures of transfusion avoidance: Gynecology and Obstetrics

Topic 22: Measures of transfusion avoidance: Trauma and injuries

Topic 23: Measures of transfusion avoidance: Hematology and Oncology

Topic 24: Measures of transfusion avoidance: Orthopedics

Topic 25: Measures of transfusion avoidance: Urology

- Topic 26: Measures of transfusion avoidance: Gastroenterology
- Topic 27: Measures of transfusion avoidance: Nephrology
- Topic 28: Measures of Transfusion Avoidance: Critical Care
- Topic 29: Measures of transfusion avoidance: Cardiothoracic and transplant Surgery
- Topic 30: Measures of transfusion avoidance: General and vascular surgery, ENT, Dental surgery

The teaching and training methods place an emphasis on practical work over passive intake of information. We will use a number of methodologies including: 1) problem-based learning in which participants are asked to take care of a simulated patient; 2) demonstrations in which equipment and techniques will be demonstrated by the instructor in the class room or in the hospital setting; 3) hands-on experiences in which the participants are allowed to work with the equipments, to try to solve a practical problem and to get acquainted with the manual work; 4) role-playing in which the participants play the role of the patient or of their workmates and practice communication skills; 5) lecturing when it is the only way to convey some ideas and will be used for providing the basic PBM information; 6) self-study, using take-home materials and training on available resources, can help the participants to find solutions for a problem and enable him to solve problems which arise after the training program; and 7) practical training in the authentic environment of the hospital or an office may be possible in selected circumstances.

Reportable Outcomes

The project team has completed Specific Aim 1, “Develop an evidence-based multimodality PBM training program. As a result, the team has conducted extensive literature review on PBM state of the art, developed a database depository of foundational literature which forms the body of knowledge supporting the field. .

The PBM Literature Depository is intended to function as a web-based publicly available searchable database of all published studies that address one or some aspects of PBM or transfusion medicine. The database is designed to capture all relevant newly published studies indexed in PubMed, as well as studies previously published in PubMed-indexed studies, starting from the more recent publications and going back.

During the time period covered by this report, specific search terms have been developed and tested to ensure that relevant literature is captured. The search terms have been run on PubMed and results have been saved, screened to exclude unrelated literature, and downloaded as text files. The text files have been ported into Microsoft Excel. The relevant literatures retrieved are organized under the following main categories:

1. Anemia management
 - 1.1. Erythropoietic agents
 - 1.2. Evaluation
 - 1.3. Hematinics
 - 1.4. Other
2. Anesthetic techniques
 - 2.1. Anesthesia
 - 2.2. Autotransfusion
 - 2.3. Fluid management
3. Blood substitutes & oxygen therapeutics
4. Blood utilization

5. Cardiology
6. Coagulopathy
 - 6.1. Evaluation
 - 6.2. Management
7. Cost-effectiveness
8. Critical Care / ICU
9. Ethics
10. GI bleeding
11. Hematology & oncology
12. Hemostatic management
 - 12.1. Drugs
 - 12.2. Surgical
 - 12.3. Topical applications
13. Immunomodulation & storage lesion
14. Massive bleeding
15. OB/GYN
16. Patient outcomes
17. Pediatrics
18. Surgical techniques
19. Thrombocytopenia & platelet impairments
 - 19.1. Evaluation
 - 19.2. Management
20. Transfusion practice
21. Transfusion risks & adverse events
22. Trauma
23. Miscellaneous

Each study can be classified under more than one category. Additionally, each manuscript in the Excel database has been classified according to its type (primary [original research] vs. secondary literature), and the primary literatures have been further scored according to the methodology of the study using the following scheme (lower score indicates higher quality of evidence):

1. Large randomized controlled trials
2. Small randomized controlled trials
3. Non-randomized trials with contemporaneous controls
4. Non-randomized trials with historical controls
5. Cohort studies
6. Case-control studies
7. Cross-sectional studies
8. Surveillance (e.g., using databases or registries)
9. Series of consecutive cases

The saved search terms in PubMed have also been configured to be automatically rerun and capture newly published studies on a weekly basis, which are treated in a similar manner as studies identified in the first run of the search terms as described above.

After evaluating various formats and methods for making the results publicly available, the format currently used by SABM (Society for the Advancement of Blood Management) to provide its Reference Library was chosen to be used as the base platform for PBM Literature

Depository. The SABM model can be seen at: <http://www.sabm.org/professionals/reference/> Additional information and an advanced search option will be provided for studies retrieved through the PBM Literature Depository.

Retrograde Literature Review and Evidence Based Depository Development

The PBM Literature Depository is designed to be a web-based publicly available searchable database of all published studies that address one or some aspects of PBM or transfusion medicine. The database is designed to capture all relevant newly published studies indexed in Pub Med, as well as studies previously published in Pub Med-indexed studies, starting from the more recent publications and going back.

To date over scholarly articles have been reviewed to create the “one of a kind” evidence based knowledge repository upon which the blood transfusion and PBM curriculum is based. The EHMC team is performing the search according to the parameters previously established and reported. The search is performed in two levels. The retrograde search covers manuscripts indexed in Pub Med from January 1, 2000 and up to Jul 2012. Over **575,000** manuscripts have been reviewed in the retrograde analysis. Here is the summary of retrograde manuscripts that have been placed into their categories:

Category	No. Articles
ANEMIA MANAGEMENT - Hematinics	527
ANESTHETIC TECHNIQUES - Autotransfusion	444
THROMBOCYTOPENIA & PLATELET IMPAIRMENTS - Management	574
COAGULOPATHY - Management	635
HEMOSTATIC MANAGEMENT - Surgical	602
TRANSFUSION PRACTICE	1630
ANEMIA MANAGEMENT - Erythropoietic agents	1166
COAGULOPATHY	244
HEMOSTATIC MANAGEMENT - Topical agents	271
THROMBOCYTOPENIA & PLATELET IMPAIRMENTS - Evaluation	123
ETHICS & LEGAL	105
MASSIVE BLEEDING	373
TRANSFUSION RISKS & ADVERSE EVENTS	1568
COAGULOPATHY - Evaluation	113
ANEMIA MANAGEMENT	738
THROMBOCYTOPENIA & PLATELET IMPAIRMENTS	156
HEMOSTATIC MANAGEMENT	425
PATIENT OUTCOMES	620
COST-EFFECTIVENESS	188
ANESTHETIC TECHNIQUES - Anesthesia	93
BLOOD SUBSTITUTES & OXYGEN THERAPEUTICS	426
ANESTHETIC TECHNIQUES - Fluid management	124
ANEMIA MANAGEMENT - Evaluation	343

In addition to developing the PBM Literature Depository database and Curriculum, the Principal Investigator and colleagues, have also been productive contributors to the growing body of peer reviewed literature and training related to PBM on a local, regional, national and international basis. They also continued their efforts to bolster awareness and outreach related to PBM in the form of scientific meetings for professionals, education for patients, and press coverage to better inform key stakeholders groups. Selected original journal articles, symposia, presentations and links to multi-modality media during the reporting period are listed in References.

Conclusion

The multi-year research project “Study of Current Practice and Future Advancements in Blood Management and Effectiveness of a Multimodality Training Program on Improving Transfusion Knowledge, Practice, and Outcomes”, has developed unique, militarily relevant curricula and evidenced based best practices in support of blood management. The study has aligned its efforts thru direct interaction with military stakeholders. The program is well positioned to explore the most effective evidenced based mechanisms to assist the DOD in integrating blood management best practices into military health system processes and procedures.

Due to significant decrease in the budget appropriated for the study, adjustments need to be considered in terms of the resident training component of the study. The initial proposal was budgeted for a five year study. The actual budget only covers three years of operation. As a consequence, the original objective of conducting three years of pre and post training skill acquisition analysis is not possible.

Based on detailed discussions with DOD and NIH blood management stakeholders an option may be to leverage the one of a kind EHMC best practices data repository and curriculum as an online resource for military research and training in an ADL (Advanced Distributed Learning) format. Many military and civilian blood management personnel may find it difficult in today's period of constrained budgets to fund a resident training course requiring over full work week to complete. An online JIT (Just in Time) training resource may be a better fit for military personnel hard pressed for training time. The evidenced based data repository may be of greater lasting value as an online resource available to military personnel as well.

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Publications

1. Shander A, Javidroozi, M, Juhl A, Naqvi S, Aregbeyen O, Demir S, Awan A Accuracy of non-invasive monitoring in Intensive Care Unit patients with very low hemoglobin. Abstract accepted for the Society of Critical Care Medicine (SCCM) 2011 Annual Meeting.
2. Moskowitz D, Aregbeyen O, Demir S, Javidroozi M, Juhl A, Naqvi S, Shander A. Impact of Aprotinin Withdrawal on Outcomes of High-Risk Cardiac Surgery - A Propensity-

3. Shander A, Farmer S, Gombotz H, Gross I, Hofmann A, Javidroozi M, Juhl A, Leahy M, Ozawa S, Sweeny J. Laying The Foundation For A Patient Blood Management Registry. Abstract accepted for the Society of Advancement of Blood Management (SABM) 2011 Annual Meeting
4. Juhl A, Aregbeyen O, Naqvi S, Demir S, Khan A, Shander A. The Autologous Transfusion Database: Englewood Hospital and Medical Center's Response to the Silent Call for Standardization of Data Collection. Abstract accepted for the Society of Advancement of Blood Management (SABM) 2011 Annual Meeting
5. Shander A, Ozawa S, Banks C.M., Sokolowski J.A., Physician training in patient blood management using immersive simulation. Abstracts of the 13th Annual NATA symposium Copenhagen, Denmark April 2012.
6. Goodnough LT, Shander A. **Patient Blood Management.** Anesthesiology. 2012 Apr 6. [Epub ahead of print] No abstract available.
7. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, Holcomb JB, Illoh O, Kaplan LJ, Katz LM, Rao SV, Roback JD, Shander A, Tobian AA, Weinstein R, Swinton McLaughlin LG, Djulbegovic B; for the Clinical Transfusion Medicine Committee of the AABB. **Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB.** Ann Intern Med. 2012 Mar 26. [Epub ahead of print]
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11. Hofmann A, Farmer S, Shander A. **Five drivers shifting the paradigm from product-focused transfusion practice to patient blood management.** Oncologist. 2011;16 Suppl 3:3-11.
12. Shander A, Juhl A, Naqvi S, Aregbeyen O, Demir S, Awan A

Abstracts

Non-invasive and continuous hemoglobin monitoring in an Intensive Care Unit patient with low hemoglobin. Abstract accepted for the Society of Advancement of Blood Management (SABM) 2010 Annual Meeting

13. Shander A, Javidroozi M, Patel M, Aregbeyen O, Naqvi S, Juhl A, Moskowitz D
The benefits of a patient blood management program in the post-aprotinin era. Abstract accepted for the Society of Advancement of Blood Management.(SABM) 2010 Annual Meeting.
14. Shander A, Javidroozi, M, Juhl A, Naqvi S, Aregbeyen O, Demir S, Awan A
Accuracy of non-invasive monitoring in Intensive Care Unit patients with very low hemoglobin. Abstract accepted for the Society of Critical Care Medicine (SCCM) 2011 Annual Meeting.

Webinars

“Fluid Management in Critically Ill Patients” webinar, Aspen Valley Hospital Aspen, CO

“Perioperative Fluid Management: Does it Improve Outcomes?” webinar, Kaiser Roseville Medical Center Roseville, CA

“Fluid Management in Critically Ill Patients” webinar, St. Francis Hospital Columbus, GA

“Fluid Management in Critically Ill Patients” webinar, Spartanburg Regional Healthcare, Spartanburg, SC

“Fluid Management in Critically Ill Patients” webinar, UMC University Medical Center Lubbock, TX

International Presentations

22nd International Congress of the Israel Society of Anesthesiologists “Active steps to avoid autologous transfusion” Tel Aviv, Israel. 9/13/11

Critical Care Canada Forum “Patient Blood Management” Toronto, ON 11/13-16.

CSL Behring satellite symposium at the World Congress of Anesthesiologists (WCA) “A critical view on safety and efficacy data of transfusion of red blood cells, plates and fresh frozen plasma”. Buenos Aires, Argentina. 3/27/12.

Masimo symposia at the WCA “Current state of patient blood management”. 3/26/12

9th Congress of Anesthesiology of Sao Paulo Meeting “Blood transfusion in oncology patients – can use the same criterium”, Myths and evidence in blood transfusion”, Perioperative management in the anemic patients”, “From bloodless surgery to blood management”, Sao Paulo Brazil 5/4/12

Open Medical Institute-MUW Seminar in Severe Bleeding Management “Patient Blood Management”, Salzburg, Austria. 7/20/12.

National Presentations

Mount Sinai Hospital “Fluid Management in Clinical Practice: One Size Does Not Fit All” New York, NY 8/25/11.

Newark Beth Israel Medican Center “Fluid Management in Clinical Practice: One Size Does Not Fit All” Newark, NJ. 10/6/11.

Chester County Hospital Critical Care Symposium “Fluid Management in Critically Ill Patients” West Chester, PA, 10/6/11

Methodist Hospital (Thomas Jefferson University Hospital) “Fluid Management” Philadelphia, PA, 11/2/11.

Palisades Medical Center “Patient Blood Management” North Bergen, NJ 11/8/11.

65th Postgraduate Assembly in Anesthesiology “What is really dangerous? Anemia or Transfusion”, New York, NY 12/12/11

St. Peter’s University Hospital “Patient blood management” New Brunswick, NJ 1/18/12.

Maimonides Medical Center “Patient Blood Management”, Brooklyn, NY, 1/18/12.

The New Jersey State Society of Anesthesiologists 53rd Annual Spring Meeting “AQI, is it for everyone” NJ, 4/21.12.

Appendix B

Study of Current Practice and Future Advancements in Blood Management and Effectiveness of a Multimodality Training Program on Improving Transfusion Knowledge, Practice and Outcomes

Study Protocol

Protocol Title

Study of Current Practice and Future Advancements in Blood Management and Effectiveness of a Multimodality Training Program on Improving Transfusion Knowledge, Practice and Outcomes

1. PI/Study Staff

- Primary Investigator/Project Director: Aryeh Shander, MD

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- Co-Primary Investigator: Mazyar Javidroozi, MD, PhD

Scientist/Director of Clinical Research, Department of Anesthesiology, Englewood Hospital and Medical Center

- Co-Investigator: Sherri Ozawa, RN

Manager/Director, Bloodless medicine and Surgery, Englewood Hospital and Medical Center

- Co-Investigator: Anna Juhl, RN

Director of Clinical Research, Department of Anesthesiology, Englewood Hospital and Medical Center

2. Study Location(s)

Englewood Hospital and Medical Center (Federalwide or DOD Assurance number)

Site Investigator: Aryeh Shander, MD (Chief, Department of Anesthesiology, Englewood Hospital and Medical Center, 350 Engle Street, Englewood, NJ 07631; Tel (201)894-3238; Fax (201)894-0585; E-mail aryeh.shander@ehmc.com)

3. Background

Allogeneic blood transfusion has been successfully used in resuscitation of severely bleeding patients and in management of patients with extremely low hemoglobin (Hb) concentration. Apart from these extreme cases, millions of patients are transfused every year, with no proven benefits. Studies have indicated substantial inter-institution and inter-practitioner differences in transfusion practices, with many transfusions being administered inappropriately [1,2].

Inappropriate blood transfusions should be avoided for several reasons [3]. First, blood transfusions are associated with risks. Some (e.g. risk of Human Immunodeficiency Virus [HIV] transmission and giving wrong blood), are well-defined and controllable at a cost, although the risk will never be zero, and the possibility of new emerging infections always exists [4]. Other risks (e.g. immunomodulation and storage lesion) are poorly defined, and are likely to be inherent to blood. A multitude of studies have reported worse outcomes in transfused patients, compared with untransfused or restrictively transfused cohorts (Table 1). The reason is not clear, and the possibility of decision to give transfusion acting as a surrogate for the overall condition of the patient has been suggested [5]. However, the association usually persist after adjusting for confounders and severity of illness.

Second, blood transfusions are very costly, and the associated cost is expected to further escalate with increasingly complicated testing and processing being performed on blood. Current estimates place the price tag of a unit of transfused blood at around US\$ 1400 [6]. The “true” cost can be much higher, since several costly consequences of transfusion (e.g. legal proceedings and compensation to patients who acquire HIV through transfusion) were not accounted for in this estimate.

Third, the blood supply is shrinking relative to the demand. Less than 5% of the eligible population in the U.S. donates blood, while the greatest pool of recipients, the elderly, continues to grow. As a result, many blood banks across the U.S. routinely operate with a very limited inventory of blood [7,8].

Four, blood has a limited shelf-life and specific processing, storage and transportation requirements. Conflicts and disasters can easily break its fragile supply chain. This further complicates the goal of maintaining a reliable and adequate blood supply for the patients who really need it. As a recent example, harsh winter weather across the U.S. in late December 2008 resulted in reports of blood shortage in many hospitals across the U.S. It is evident that blood

supply remains a major vulnerability of our nation's health care system, putting many lives in danger.

For these reasons, minimizing and avoiding unnecessary allogeneic transfusions is likely to be beneficial for most patients. Subsequently, many techniques and approaches used in the management of patients for whom allogeneic transfusions are not an option (e.g. those who refuse blood transfusions on religious grounds) have been successfully used to care for other patients, in what has become to be known as Patient Blood Management (PBM) [9]. Here, the goal is not merely avoiding or withholding transfusions, but timely application of evidence-based medical and surgical concepts designed to manage anemia, optimize hemostasis, and minimize blood loss and blood transfusions in order to improve patient outcomes. As such, all patients – regardless of their preference or acceptance of blood products – can be considered as candidates for PBM.

The concept of PBM is evolving. Earlier definitions involved the appropriate provision and use of blood, its components and derivatives, and strategies to reduce or avoid the need for a blood transfusion, with the ultimate goal of improved patient outcome [10]. The newer concept places more emphasis on preventative measures that will obviate the need for transfusions (i.e. by relying on patient's own blood rather than donor's blood). Given the negative outcomes of inappropriate transfusions, blood transfusion has been proposed as a quality indicator in surgery [11]. Considering the promising benefits of PBM strategies for patients and the health care system, it is hoped that PBM is increasingly viewed and adopted as a standard of care for all patients who may be at risk of being transfused at any time during their care.

Studies have shown that the vast majority of transfusions (as many as 94%) in surgical patients can be attributed to one or a combination of the following factors: low preoperative hemoglobin levels, excessive surgical blood loss, and inappropriate transfusion practices [10]. To this end, PBM relies on three corresponding aspects, the “pillars” of PBM (Figure 1) [12,13]:

- optimizing hematopoiesis
- minimizing bleeding and blood loss, and
- harnessing and optimizing physiological tolerance of anemia through application of all available modalities, leaving transfusion as be the last resort.

Examples of the suggested PBM strategies that can be considered during pre-, intra- and postoperative care of a general surgical patient are depicted in Figure 2 [14]. It should be noted that while PBM strategies are commonly aligned with the perioperative management of

patients, many strategies are also applicable to the non-surgical patient populations, and should be considered in the care of these patients as well.

Some of the most effective measures used in PBM (e.g. evidence-based transfusion practice; management of anemia with iron/folate/B12) are safe and associated with little (if any) cost. Some other measures are more controversial. PBM and modalities used in it are quickly evolving, as reflected in the recent changes in labeling of erythropoiesis-stimulating agents (ESAs) and emerging local hemostatic agents [15,16]. Therefore, a blood management program needs to be continuously updated to reflect the most recent evidence on the safety and efficacy of its individual modalities. Similarly, cost-effectiveness of each PBM modality is subject to investigation and should be addressed individually.

A number of experiences indicate the efficacy of blood management in reducing transfusion rate without compromising patient outcomes. Since 1993 and following implementing a comprehensive multimodality PBM program at Englewood Hospital and Medical Center (EHMC), the number of RBC units transfused per “at risk” surgical patient at EHMC has steadily declined (Figure 3) [14]. Despite the low transfusion rates, mortality and perioperative adverse events matched for illness severity were unaffected in the same period [17]. Other studies on implementation of blood PBM in other centers have had similarly encouraging results [18,19].

Evidence supports wider implementation of PBM programs. Since 2002, a PBM initiative was implemented in 23 hospitals in Ontario, Canada through appointing transfusion coordinators under ONTraC program. After 12 months, there was an overall 14% to 24% reduction in blood use in the target patient populations and the reductions continued over the 24-month period of the project. In the same period, incidence of infections and length of stay decreased [20]. A controlled trial in Canada in which 14 hospitals were randomized to a comprehensive PBM algorithm and 15 hospitals were randomized to standard care has also showed that the transfusion rate in the target patient population was 9.6% lower in the PBM hospitals [21]. A smaller cluster-randomized trial was conducted in India in which 12 hospitals were randomized to use of a simple, self-educating transfusion request form or no intervention. In this study, the number of transfusion requests per admission decreased in the hospitals randomized to the self-educating form, but the effect was small, and it was attributed to the limited nature of the intervention [22]. The present study is intended to provide participants with a multimodality training program designed to provide them with the information

necessary to implement PBM into their clinical practice, and effectively build and manage a PBM program.

Table 1- Outcomes of allogeneic blood transfusion.

Setting/Population	Outcomes associated with transfusion	Reference
Cardiac surgery	Increased mortality rate; Longer ICU stay Higher incidence of bacterial infection Increased 5-year mortality rate; Higher incidence of serious postoperative infections Higher risk of developing AF Increased mortality rate; Higher risk of renal failure, prolonged respiratory support, serious infection, cardiac complications and neurologic events Reduced long-term survival Delayed discharge from hospital; Higher risk of death within 30-day; Higher risk of infection; Higher risk of ischemia	Leal-Naval (2001) Chelemer (2002) Engoren (2002) Koch (2006) Koch (2006) Koch (2006) Murphy (2007)
Colorectal surgery	Higher risk of postoperative infection and intra-abdominal sepsis	Chang (2000)
ICU/Critically ill patients	Increased overall and ICU 14-day mortality rate; Higher 28-day mortality rate Increased mortality rate; Longer length of stay; More total number of complications Increased mortality rate; Higher risk of developing ARDS Higher incidence of bloodstream infections Higher risk of nosocomial infection Higher risk of developing ARDS Increased hospital mortality rate; Prolonged hospital stay	Vincent (2002) Corwin (2004) Gong (2005) Shorr (2005) Taylor (2006) Zilberberg (2007) Zilberberg (2008)
Myocardial infarction/ischemia	Increased 30-day mortality rate if hematocrit on admission was > 36% Increased 30-day mortality Increased risk of in-hospital mortality	Wu (2001) Rao (2004) Jani (2007)
Orthopedics	Higher risk of bacterial infection; Higher risk of pneumonia Higher risk of infection Longer time to ambulation; Longer length of stay	Carson (1999) Innerhofer (2005) Weber (2005)
Subarachnoid hemorrhage	Higher risk of vasospasm and poor outcome	Smith (2004)
Trauma	Higher risk of developing infection Increased mortality rate; Higher risk of ICU admission; Longer ICU and hospital length of stay Increased mortality rate; Higher risk of ICU admission; Higher incidence of SIRS Increased mortality rate; Higher risk of developing ARDS	Claridge (2002) Malone (2003) Dunne (2004) Silverboard (2005)

AF, atrial fibrillation; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome.

Figure 1- Pillars of Patient Blood Management [12,13].

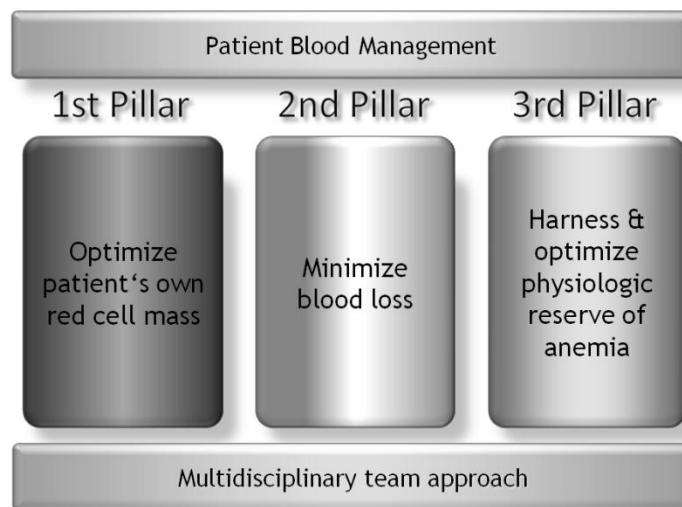


Figure 2- Examples of blood management strategies considered during care of a general surgical patient. Many strategies can also be used in care of non-surgical patients [14].

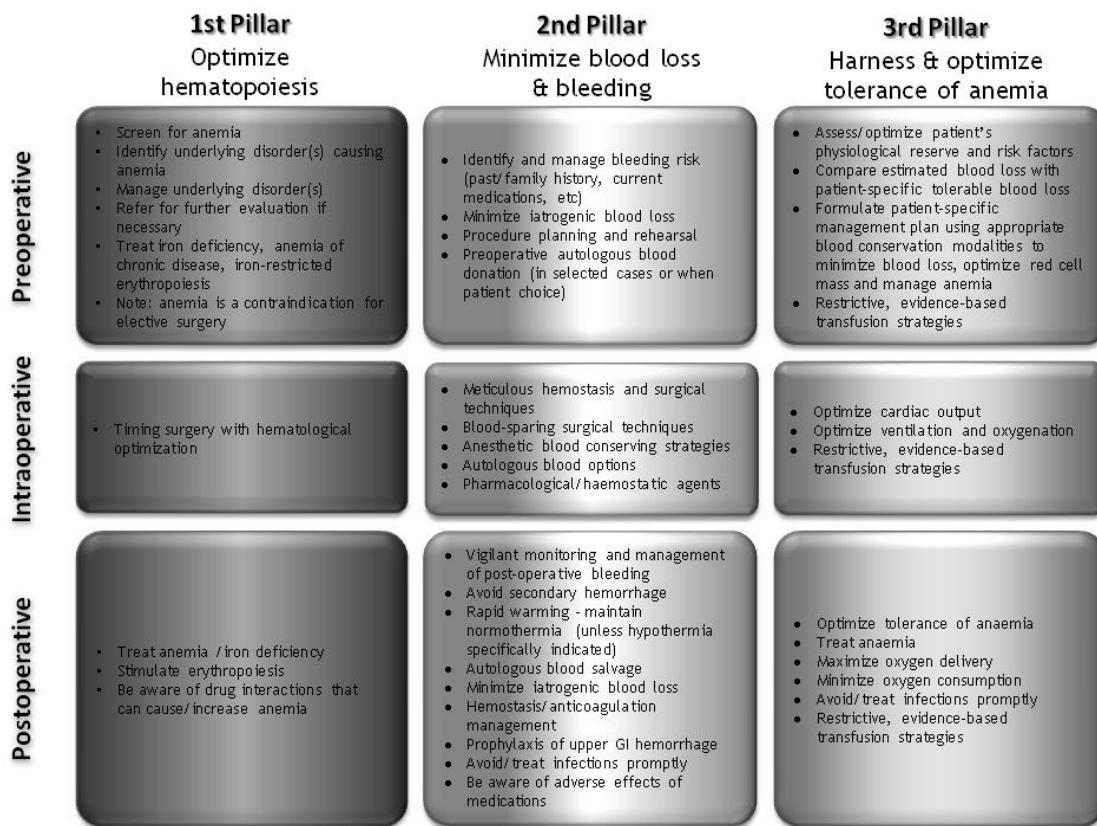
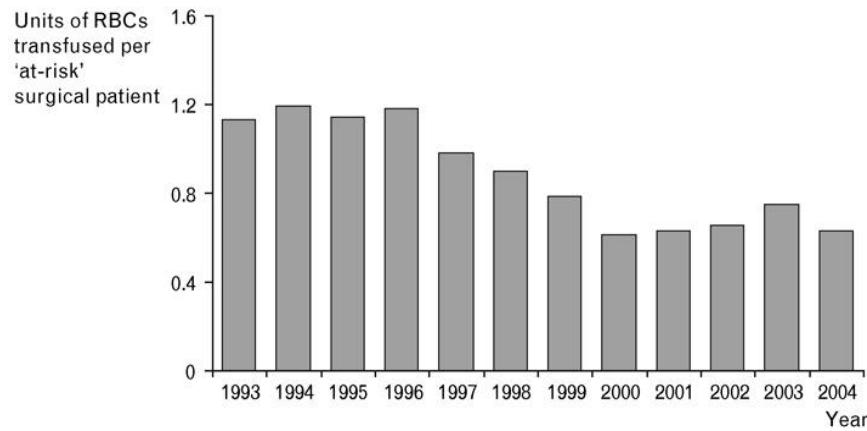


Figure 3- Number of units of red blood cells (RBCs) transfused per 'at risk' surgical patient by year at Englewood Hospital and Medical Center (EHMC). Relative increases seen in 2002-03 have been attributed to an influx of new intensivists whose transfusion practices were modified to conform to EHMC's approach [14].



4. Objectives/Specific Aims/Research Questions

This study intends to accurately measure and compare the PBM knowledge of the participants before and after the PBM training program. The hypothesis is that the PBM training program improves PBM knowledge of the participants, as quantified by the study pre- and post-tests.

5. Research Design

This study is based on validated surveys administered prior and after the PBM training program to assess the PBM knowledge of the participants. Study participants are identified and recruited from clinicians who routinely make transfusion decisions, or are involved in transfusion-related administrative duties, from a pool of hospitals. All participants will be subject to the same data collection procedures as well as the same training program(i.e., no control group in planned). Pre-training data on the participants (demographics, academic and professional background, transfusion and PBM knowledge data as quantified using validated surveys) is collected from the participants. Participants are invited for the PBM training program. Additional data on the PBM knowledge of the participants is collected on the first day of the training, during the training on daily basis, and at the conclusion of the training program before the participants leave the program. Post-training data is collected on the PBM knowledge of the participants after the training.

5.1. Study Endpoints

- Weighted score on the PBM fixed tests
- Weighted score on the PBM randomly selected tests
- Weighted score on the fixed PBM case-based assessment
- Weighted score on the randomly-selected PBM case-based assessment
- Weighted total score

5.2. Reliability and Validity of Surveys

The survey's reliability and validity will be determined as previously defined for instruments for evaluating education in evidence-based practice [23,24], with particular attention to specific considerations of multiple choice questionnaires [25]. To establish reliability and validity, both pilot testing as well as analysis of participants' scores will be used as described here.

5.2.1. Interrater reliability

Since the surveys will be in multiple choice question format with previously established and verified answer keys and no rater judgment is required to score, it is not applicable to this study.

5.2.2. Validity

5.2.2.1. Based on Content

Content and face validity will be established through review of the survey by PBM experts not involved in development of the surveys. If necessary, adjustments will be made to the surveys to achieve content validity.

5.2.2.2. Based on Internal Structure

5.2.2.2.1. Internal Consistency

Internal consistency will be evaluated for each section of the survey (i.e. questions relating to each module/topic of curriculum) independently using Kuder-Richardson coefficient, a form of commonly used Cronbach's alpha used for dichotomous data (answer of questions scored as "correct" or "incorrect"), based on participants' data as well as pilot testing. An alpha of 0.7 or more will be required to establish consistency and adjustments to survey will be made if necessary.

5.2.2.2.2. Dimensionality

Since the surveys for this study are designed to quantify participants' knowledge in various topics under PBM, multiple dimensions are expected to exist in the questionnaires. Exploratory factor analysis will be done on participants' scores to evaluate the dimensionality of the surveys and questions that are correlated with each other.

5.2.2.3. Based on Relationship to other Variables

5.2.2.3.1. Responsive

The survey is expected to detect the impact of PBM training program on knowledge of the participants. To establish

responsiveness, the score of same participants in endpoints listed in Section 6.1 before and after the PBM training will be compared using paired statistical tests.

5.2.2.3.2. Discriminative

The ability of the surveys to discriminate between participants with different levels of PBM expertise will be evaluated through statistical comparison of survey scores among participants of different baseline levels of PBM expertise (self proclaimed), as well as in pilot testing among volunteer with various levels of PBM expertise. Additionally, item-to-total correlations will be evaluated for each individual question during pilot testing and questions with negative or zero discrimination will be excluded or revised.

5.2.2.3.3. Criterion

Since no other similar instruments with established psychometric properties is available at time of development of this study, statistical test of the relationship between the participants' scores on this and another survey is not planned.

6. Study Population

Study participants are identified and recruited from clinicians who routinely make transfusion decisions, or are involved in transfusion-related administrative duties, from a representative selection of hospitals.

7. Inclusion/Exclusion Criteria

For this study, independent eligibility criteria apply to the potential participants and centers where potential participants practice.

7.1. Center Eligibility Criteria

To be considered for this study, a center should have a blood bank facility (can be off-premise) and it should have at least one department that use transfusion as part of care.

7.2. Participant Eligibility Criteria

Each participating hospital will be asked to select 2 staff members and forward their information to the study personnel. The selected staff members should meet the following criteria:

- A. One staff member should be a fully licensed clinician working at a department/service which routinely administers blood transfusions to the patient.
- B. The other staff should be someone with clinical training and background (e.g. physician, nurse, pharmacist, etc) who has an administrative role in the hospital.
- C. Staff members must be permanent employees of the hospital or medical groups working at hospital (no temporary/contract staff).
- D. Staff members should have no disciplinary actions in their records and not be in probation.
- E. Staff members must be willing to participate in the study, including agreeing to fill out and return the surveys on a timely manner.
- F. Staff members should be able to travel to the Englewood Hospital and stay for the duration of the training.
- G. Staff members should be willing to train other staff members at their hospital with regards to PBM, should such a training is requested by their hospital administrators.

A staff member meeting both A and B criteria may be substituted for two staff members, although participation of two different staff from each hospital is preferred and encouraged.

8. Description of the Recruitment and Screening Process

Centers meeting the eligibility criteria listed under Section 8.1 will be identified from the following sources, with preference given in the order given:

- A- Selected hospitals that at anytime have expressed interest in PBM as demonstrated by contacting SABM, or taking steps toward implementing a PBM or similar program;
- B- Selected hospitals identified and recommended by the Funding agency; and

C- Hospitals randomly selected from American Hospital Association (AHA) U.S. hospitals database.

Selection of the group-C centers will be done through cluster randomization of the AHA hospitals, with stratification for the number of beds, geographical region, and academic/community-based status. In each cluster, centers will be randomly selected and contacted.

For each selected center, the following general procedure will be followed (subject to modification based on the existing liaison and collaboration with centers):

1. First contact will be a package mailed to the hospital administrating office, introducing the project and providing introductory data as well as contact information for further discussion.
2. A follow-up phone call approximately 2 weeks after delivery of the first package if the hospital has not contacted first.
3. Additional information on the study (including objectives, methods and expected commitment) will be provided and any questions or concerns will be answered via telephone talks and eligibility of the hospital will be reconfirmed (presence of blood bank facility, routine transfusions).
4. Once all questions of the hospital are adequately addressed, and the hospital agrees verbally to participate in the study, the hospital will be asked to:
 - a. Sign a letter of intent expressing their agreement to participate and support their staff who will be participating in this study.
 - b. Review the study by their respective IRB or ethics committee and obtain a confirmation that no formal approval is needed for the study, or if an approval is deemed necessary, complete the application and obtain the required IRB approval to participate in this study.
 - c. Select 2 permanent staff who are willing to participate in the study on behalf of the hospital, according the participants eligibility criteria cited below, and forward their names and contact information to the study personnel.

Each consenting participating hospital will be asked to select 2 staff members and forward their information to the study personnel. The selected staff members should meet the eligibility criteria listed under Section 8.2.

9. Description of the Informed Consent Process

The selected candidates will be contacted by the study staff to determine interest and availability, and to confirm the collected data. An informed consent form will be offered to the candidates and all their questions regarding the study and related issues will be fully addressed prior to obtaining the consent.

10. Study Procedures/Research Interventions

Pre-training data on the participants (demographics, academic and professional background, transfusion and PBM knowledge and practice) is collected from the participants. Participants are invited for the PBM training program. Additional data on the PBM knowledge of the participants is collected on the first day of the training, during the training on daily basis, and at the conclusion of the training program before the participants leave the program. Post-training data is collected on the PBM knowledge of the participants after the training.

PBM knowledge data collection will be performed using validated survey (as described under Section 6.2) administrated before and after the training courses. Additionally, participants' data deemed necessary for this study will be collected as part of administered surveys. The surveys will be structured as follows:

1. Introduction and general instructions
2. Demographics survey
 - a. Personal data
 - b. Academic background
 - c. Professional background
 - d. Previous/other PBM/transfusion training
 - e. Current practice/role information
3. PBM tests (60 fixed and approximately 100 randomly selected questions)
 - a. Instructions
 - b. Definition and Organization of PBM
 - c. Anemia and Hematopoiesis Optimization (1st Pillar)
 - d. Minimizing Blood Loss: Systemic Hemostasis (2nd Pillar)

- e. Minimizing Blood Loss: Surgical and Radiological Approaches (2nd Pillar)
 - f. Minimizing Blood Loss: Autologous Transfusion (2nd Pillar)
 - g. Minimizing Blood Loss: Anesthesiological Considerations (2nd Pillar)
 - h. Optimizing Tolerance of Anemia in Surgery (3rd Pillar)
 - i. PBM in Critical Care
 - j. PBM in Gastrointestinal Bleeding
 - k. PBM in Pediatrics
 - l. PBM in Gynecology and Obstetrics
 - m. PBM in Orthopedics
 - n. PBM in Emergencies
 - o. PBM in Trauma
 - p. PBM in Cardiology
 - q. PBM in Hematology and Oncology
4. PBM case-based assessments (1 fixed and 2 randomly selected cases, approximately 90 questions in total)
- a. Instructions
 - b. Case 1
 - c. Case 2
 - d. Case 3

The PBM tests will be primarily in form of independent multiple-choice questions and true/false statements. The case-based assessment will include multiple-choice questions integrated in various steps of care of hypothetical cases. All questions and cases will be designed and developed by experts in PBM to ensure clinical relevancy. Additionally, generally accepted aspects of designing evaluations (including those for multiple-choice question) will be considered and applied in designing the tests for this project [25-30]. Namely, questions will be designed to address knowledge, comprehension, and/or application. The stem verbage will be concise, positive, and clear with proper choice of strong action verbs. Answer set will include distractors (incorrect responses, usually 3) and one keyed correct response. Using answers such as “All of the above” or combined answers (e.g. 1 and 2) will be avoided. Answer sets will be arranged logically, such as increasing or decreasing values, with each answer approximately the same length. Every item will provide reference ranges and units while avoiding abbreviations as much as possible.

Considering the possibility that completing a specific test may influence the performance when repeating the same test, participants will take different sets of tests with comparable levels of difficulty before and after training, in addition to fixed (unchanged) questions. To achieve this goal, a large pool of questions will be developed by the study team, and all questions will be pre-tested by several volunteers meeting the selection criteria of the study participant, who have not been directly involved in developing the questions to assess face and content validity, comprehensibility, time to completion, and ambiguity. The pre-testers will also be asked to rate the difficulty of each question on a scale of 1 to 3 (1 being the easiest and 3 being the most difficult). The median rating of each question will be taken as the difficulty level of that question (1=easy, 2=medium, 3=difficult).

Similar pre-testing will be performed for the case-based assessments, and after determining the difficulty level of each question, the sum of the difficulty levels of all questions within each case will be calculated, and the cases will be revised by eliminating the most difficult questions from cases with highest cumulative difficulty, to ensure that all cases have comparable overall difficulty. If substantial variation in cumulative difficulty levels of various cases is noted, requiring elimination of large number of questions, cases may be grouped in 2 or 3 difficulty levels.

For each participant, 2 complete set of tests will be prepared, by randomly selecting questions from the pool until the sum of the difficulty levels reach 200 (equivalent of 100 medium-difficulty questions) in addition to 60 fixed questions. Two cases will also be randomly selected form the pool of case-based assessments in addition to a fixed case. If different difficulty levels were assigned to different cases, cases will be randomly selected from each difficulty level to ensure uniform distribution of cases with various difficulty levels among participants and before and after the training.

Each correct answer will be given one point and each wrong answer will get zero point. All scores will be weighted by the difficulty level of the respective question.

The pre-tests will be administered in a window between 3 to 1 months before the schedule beginning of the training. The participants will be instructed to solely rely on their knowledge, and resource(s) they routinely use in their practice/work to answer the questions. The tests may be completed in several sessions, but the participants will be asked to time

themselves and report the total time taken to complete the tests. The post-tests will be administered in a window between the 1 and 3 months after the training, in a manner similar to the pre-tests.

The confidentiality of all test scores will be strictly maintained and the individual scores of participants will not be disclosed to others. Similarly, all study results will be checked to ensure that their dissemination cannot result in potential disclosure of individual scores.

The study team will keep contact with participant during pre-testing to address any potential issues, and ensure timely completion of the tests. If a participant failed to complete and submit the test within the window, an extra 5 working days will be given to the participant, and if the test results are not returned, the participant will be excluded from the study.

Similarly, reasonable efforts will be made to minimize non-responders and drop-outs in the post-test data collection. The preferred format of all testing is electronic format, unless participants do not have the required infrastructure, in which case paper-based tests will be used to avoid bias.

11. Description of Protocol Interventions

The protocol intervention is the PBM training program provided to the participants during a 5-day visit to Englewood Hospital and Medical Center. The curriculum is provided as an attachment to the protocol.

12. Laboratory Evaluations

None is planned for this study.

13. Sample Size Justification

Given the structure of this study and logistics involved with the training course, the number of participants will be primarily dictated by the available funding. The original application specified 90 participants in the 3rd years, 90 participants in the 4th year, and 60 participants in the 5th year for a total of 240 participants.

Using paired t-test comparing the test scores before and after the training, and assuming an alpha of 0.05 and power of 80%, the detectable alternative will be equal to ~18.1% of the standard deviation of the pre/post-test difference. That is, assuming a maximum score of 500 on each test, and a standard deviation of 50 for the score difference between the pre- and post-test of the participants, a sample of 240 is likely to detect a difference of at least 9.1 (50×0.181) between the scores of the pre- and post-tests. Smaller sample size would increase the detectable alternative; the percentage will be 19.9% (n=200), 21% (n=180), 23% (n=150), and 25.8% (n=120), and 29.9% (n=90). The investigators consider the increased values still acceptable for this study.

14. Data Analysis

Validity and reliability of the tests will be assessed and established as described under Section 6.2 using data from volunteers as well as participants. Following collecting the data from the participants, descriptive statistics will be used to summarize characteristics of the study participants and their respective backgrounds. Pre- and post-test scores will be compared using paired t-test general linear models or proper non-parametric tests if needed. Correlation between various demographic characteristics and educational/professional backgrounds and knowledge before and after the training will also be analyzed using linear regression analysis. If necessary, variables will be transformed for better distribution and model fitting. Results of the statistical tests will be considered to be statistically significant when $p < 0.05$. Additional statistical analysis may be performed as necessary.

15. Data Management

All data will be collected using surveys described in Section 11. The study endpoints (Section 6.1) will be based on participants scores in the surveys taken before and after the training. The surveys are provided as attachments to this protocol.

The confidentiality of all test scores will be strictly maintained and the individual scores of participants will not be disclosed to others. Similarly, all study results will be checked to ensure that their dissemination cannot result in potential disclosure of individual identities or scores. Access to the study's research records and data will be limited to the study personnel listed in Section 2 and Section 18, as well as representatives of USAMRMC. any reporting of

the confidential data required under applicable laws and regulations will be performed as necessary.

Original surveys filled by the participants will be stored in locked cabinets/offices at Englewood Hospital and Medical center for at least 2 years from completion of the study, with access restricted only to authorized personnel.

16. Risk/Benefits Assessment

This study is expected to be associated with no more than minimal risk. The foreseeable risks to the participants is minimal. The recruitment process (Section 9) will be performed in a manner to ensure no risk (e.g. professional/vocational) to the participants. Their scores in the study surveys will remain strictly confidential and not disclosed to their center or other entities, with exception of what is described under Section 16. No potential risk to the study personnel is identified. No potential risk to the patients treated by the participants is identified as the PBM training program is based on evidence-based standard of care as practiced at Englewood Hospital and Medical Center.

This study has the potential benefit of providing the participants with a state of art training in PBM that could contribute positively to their patients, and other patients seen and treated at their centers, particularly if the participants succeed in promoting PBM in their home centers.

17. Study Personnel

- Roles and Responsibilities of Key Study Personnel
- Conflict of Interest

18. Roles and Responsibilities of Medical Monitor

This study is expected to be associated with minimal risk, and as such, a medical monitor is not required.

19. Withdrawal from the Protocol

Participants may discontinue participation in the study at any time without penalty or loss of benefits to which they are otherwise entitled. The study investigators may also terminate the participation of any volunteer in the study due to safety issues or non-compliance. In either case, any data already collected and available may be used. Any withdrawal will be reported to the IRB.

20. Modifications to the Protocol

Upon initial IRB approval, no modification of this protocol is allowed without a formal amendment. Any modification to the protocol, consent form, surveys, change to the PI, changes in study design, and addition or widening of a study population must be submitted to the IRB as well as the HRPO. All protocol amendments must be issued, signed and dated by the Primary Investigator. Protocol amendments must not be implemented without prior IRB and HRPO approval, or when any relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazard to the participants, in which case the amendment must be promptly submitted to the IRB, HRPO, and the relevant competent authority. When the changes involve only logistic or administrative aspects of the study, the IRB only needs to be notified.

21. Protocol Deviations and Violations

In situations requiring a departure from the protocol, the primary investigator will be contacted (preferably, before implementing any departure from the protocol), and the data recorded in the surveys will reflect any departure from the protocol.

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB. Upon discovery or notification, the primary investigator is responsible for reporting protocol deviations to the IRB.

A protocol violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the

study data. If the deviation meets any of the following criteria, it is considered a protocol violation in this study:

- The deviation has harmed or posed a significant or substantive risk of harm to the participant (e.g. breach of confidentiality).
- The deviation compromises the scientific integrity of the data collected for the study (e.g. enrollment despite not meeting the eligibility criteria, failure to treat subjects per key protocol procedures, changing the protocol without IRB approval, irreplaceable loss of data).
- The deviation is a willful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s) (e.g. failure to obtain timely ICF, data falsification, performing tests or procedures beyond the individual's scope pr privilege status).
- The deviation involves a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures (e.g. expired license, repeated deviations).

Any protocol violations must be promptly submitted for full board IRB review.

22. Reporting of Serious Adverse Events and Unanticipated Problems

Since no patient will receive medical treatment under this protocol, reporting of serious adverse events is not applicable to this study.

Unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study and all volunteer deaths related to participation in the study should be promptly reported by phone (301-619-2165), by e-mail (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the U.S. Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office. A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-P, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

23. Continuing Review and Final Report

A copy of the approved continuing review report and the local IRB approval notification will be submitted to the HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the HRPO as soon as these documents become available.

24. USAMRMC Volunteer Registry Database

Since this study is not expected to be associated with greater than minimal risk to the participants, completion of data sheets for entry into the USAMRMC Volunteer Registry Database is not required.

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